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APPLICATION NO. 0877329, 970	FILING DATE 12/02/96	FIRST NAMED INVENTOR WOUDENBERG	ATTORNEY DOCKET NO. 16842-704
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18M2/0530

EXAMINER HORLICK, K

ART UNIT 1807	PAPER NUMBER 22
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DATE MAILED: 05/30/97

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.
08/752,973

Applicant(s)
Woudenberg et al.

Examiner
Kenneth R. Horlick

Group Art Unit
1807



☒ Responsive to communication(s) filed on Feb 7, 1997

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire three month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 13-23, 26-34, and 39-42 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 13-23, 26-34, and 39-42 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been
☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 20

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

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1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 13-23, 26-34, and 39-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al. in view of Higuchi et al. (1992).

Claims 13-23 are drawn to an apparatus comprising: a sample holder; a fiber optic cable; a lens co-axially disposed with the fiber optic cable; and a detection and analysis mechanism for measuring the intensities of a first and second fluorescent signal and producing a plurality of corrected intensity signals. Claims 26-34 and 39-42 are drawn to methods comprising: taking a sample holder containing a nucleic acid sequence to be amplified, a first fluorescent indicator which produces a first fluorescent signal proportional to a concentration of the amplified sequence, and a second fluorescent indicator which produces a second fluorescent signal proportional to a volume of sample; measuring the intensities of the first and second signals; performing at least one amplification; measuring the intensities of the first and second signals; and monitoring the formation of amplification product in real time by calculating a corrected intensity signal corresponding to a ratio between the two intensities before and after amplification.

Lee et al. teach a method comprising: taking a sample holder containing a nucleic acid sequence to be amplified, a first fluorescent indicator which produces a first fluorescent signal proportional to a concentration of the amplified sequence, and a second fluorescent indicator which produces a second fluorescent signal proportional to a volume of sample; performing PCR amplification; removing the sample from the amplification vessel; and measuring the intensities of the

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first and second signals (see entire reference). With respect to claim 42, the first and second fluorescent indicators of Lee et al. are covalently attached to an oligonucleotide capable of hybridizing to the amplification product (see esp. Fig. 2 on page 3762). At the top of page 3763, second column, Lee et al. suggest that the fluorescence from one of the indicators, TMR, be used "as an internal fluorescence reference to control for pipetting errors and evaporation during thermal cycling." Further, in the final paragraph on page 3766, Lee et al. teach that "[a] homogenous system has several obvious advantages relative to an analysis method requiring separation", and that the transfer of reaction mixtures from the PCR tube to a cuvette in their procedure "is not intrinsic to the method". Consequently, Lee et al. then suggest such a homogenous system, wherein "fluorescence can be detected directly in the reaction vessel".

Lee et al. do not teach a real time detection method nor an apparatus therefor, particularly one based on fiber optics. Lee et al. also do not teach detection using a complex-forming dye as the first indicator.

Higuchi et al. (1992) teach the use of a complex-forming fluorescent dye and a fiber optic interface in the continuous, real-time monitoring of a polymerase chain reaction (PCR) amplification reaction (see especially page 415).

One of ordinary skill in the art would have been motivated to follow the suggestion of Lee et al. to detect fluorescence directly in the reaction vessel because Higuchi et al. (1992) taught a fiber optic means and method for doing so. The skilled artisan also would have been motivated to use a second fluorescent indicator in the method of Higuchi et al. as an internal fluorescence standard because Lee et al. taught that this had the advantage of compensating for "pipetting errors and evaporation during thermal cycling". In other words, the skilled artisan would have been motivated to combine the teachings of the cited references in order to achieve the combined advantages of the real-time assay and apparatus therefor of Higuchi et al., and the internal fluorescence standard of Lee et al. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to carry out the claimed methods, and to make the claimed apparatus.

2. The arguments of the response filed 02/07/97, as they apply to the amended and new claims, have been fully considered. While the arguments of paragraphs I-VI and VIII have been found

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persuasive, that of paragraph VII has not. In response to paragraph VII: (1) Higuchi et al. do in fact teach monitoring the formation of a nucleic acid amplification reaction product in real time; and (2) Lee et al. teach the existence of the problem being solved by the present invention - that the base line fluorescence of a single sample will vary over time due to system based variations (see page 3763, top of second column) - as well as the solution of using an internal fluorescence standard to account for such variations. Thus, while the response points out what teachings the individual references lack, it does not provide a convincing reason as to why the combined teachings of the cited references do not render the claimed invention prima facie obvious.

3. No claims are allowable over the prior art.

4. Livak et al. (5,538,848), Stefano (5,556,751), Walker et al. (5,593,867), and Nadeau et al. (5,547,861) are made of record as references of interest because their subject matter involves real-time monitoring of amplification reactions.

5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Kenneth Horlick whose telephone number is (703) 308-3905. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached at (703) 308-1152.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

6. Papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number for Art Unit 1807 is (703) 305-7401.

KENNETH R. HORLICK
PRIMARY EXAMINER
GROUP 1800

Kenneth R. Horlick, Ph.D.
5/20/97